

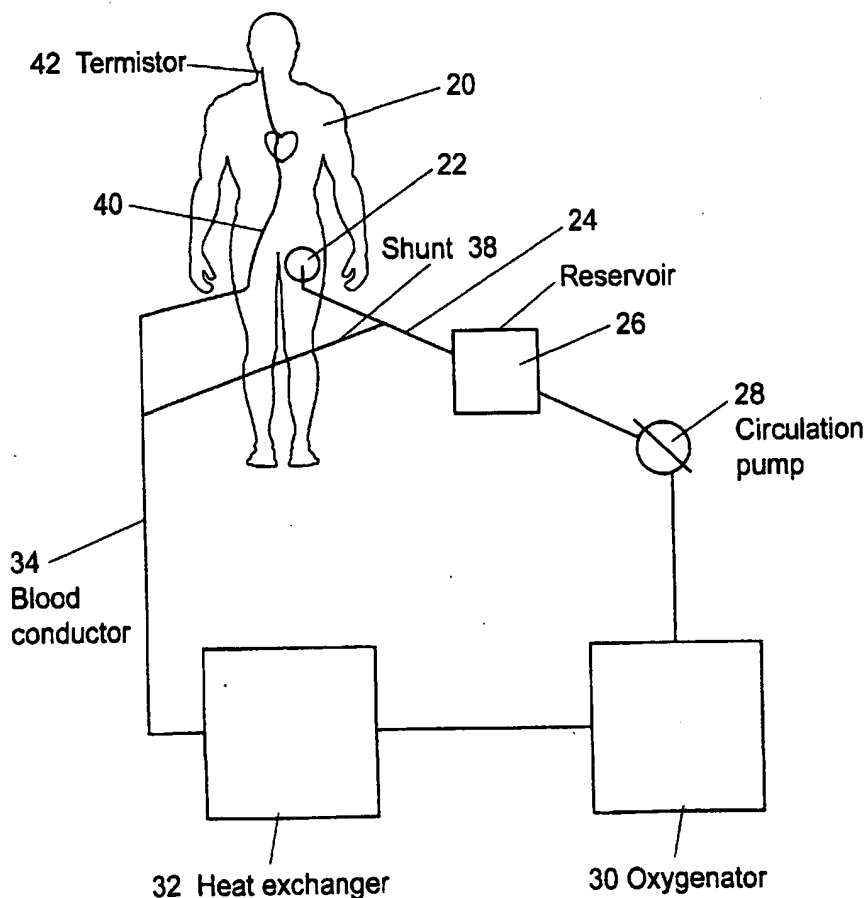
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ARGMED KOMMANDITBOLAG [SE/SE]; Parkallén
15, S-237 36 Bjärred (SE).(84) Designated States (*regional*): ARIPO patent (GH, GM,
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(75) Inventors/Applicants (*for US only*): **ALLERS, Mats**

[Continued on next page]

(54) Title: METHOD AND APPARATUS FOR CEREBRAL TEMPERING



(57) Abstract: The present invention relates to a system and a method for controlling the temperature of a selected brain hemisphere, to maintain a low temperature in the selected brain hemisphere. When used in conjunction with the treatment of stroke, the present invention comprises cooling the stroke-affected brain hemisphere during the time necessary to make a diagnosis and provide medication, and during the time necessary for the ischaemic part of the brain to recover. The present invention also provides for oxygenation of the blood before it is cooled and reintroduced into the patient.

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IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

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- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

Method and apparatus for cerebral tempering.

TECHNICAL FIELD

The present invention relates to a system and a method for controlling the
5 temperature of a selected brain hemisphere of a living being.

BACKGROUND OF THE INVENTION

In pathological conditions, the body temperature or the temperature of body parts of a living being influences the healing process and the risk of permanent damage. Cancer
10 cells, for example, are heat sensitive, and a local heating of the blood flow around a cancer tumour may for some types of cancer constitute a treatment resulting in restrained tumour growth, or in some cases even in a shrinking of the tumour. In other cases cooling of a body part may be important to reduce adverse secondary symptoms of the pathological condition.

15 In the case of a stroke, the blood flow in the brain is reduced because of a haemorrhage or a clogging of a blood vessel. This condition is critical and it is important that treatment be initiated in an early stage, to reduce the loss of bodily functions, such as paralysis. It is well known that cooling the patient reduces the metabolic turnover in the brain, which in turn lowers the release of harmful signal substances. This may prevent such
20 damage to the blood-brain barrier as could lead to the death of brain cells. A cooling of the patient therefore also results in a reduction of the symptoms of neurological deficit. However, there are certain problems associated with the cooling of an entire patient. One is that the cooling takes a considerable amount of time, another that it must be carried out under anaesthesia, and a third that there is a risk of cardiovascular complications when the
25 patient is reheated.

There are several methods in the prior art to carry out a more isolated cooling of a single organ or body part. An example of cooling of the brain is disclosed in patent document WO 98/23217, relating to a method of cerebral retroperfusion and retroinfusion, involving the cooling of arterial blood which is then returned to the entire brain. However,
30 this method entails a large and complicated surgical procedure, which delays the onset of treatment. In cases where the primary objective is to lower the temperature of one of the hemispheres of the brain, cooling the entire brain also means a certain loss of efficiency.

The American patent document US 5 906 588 discloses a method and a device for heart-lung bypass and cooling of a specific body part. This disclosure primarily relates to
35 complicated heart surgery and organ transplantations.

PURPOSE OF THE INVENTION

The purpose of the present invention is to provide a system and a method for simple, quick and efficient control of the temperature of a selected brain hemisphere.

Another purpose of the invention is to provide a system and a method for quick and simple cooling that also supports diagnostic measures such as magnetic resonance imaging (MRI), i.e. cooling without inserting metal components into the body of the patient.

5 BRIEF DESCRIPTION OF THE INVENTION

According to the invention the purpose indicated above is achieved by establishing an extra-corporeal blood conduit from a vein, preferably in the lower half of the body, modifying the temperature of the blood outside the body, and returning it through an artery, e.g. the arteria carotis communis, sinister or dexter, or some other artery that
10 supplies blood to the selected brain hemisphere. This accomplishes a quick temperature change in the selected brain hemisphere, involving only a comparatively minor surgical procedure.

When treating for example a case of stroke, the affected brain hemisphere can be cooled quickly according to the method of the invention, resulting in a reduction of the
15 symptoms of functional loss. Preferably, continued cooling is maintained in order to keep the temperature of the brain hemisphere lowered for as long as it takes to diagnose, medicate and restore the functions of the ischaemic brain section.

A further embodiment of the invention involves, in addition to cooling or heating the blood, oxygenation of the blood to improve oxygenation of the selected brain
20 hemisphere.

The invention comprises a system, equipment components and a method.

DESCRIPTION OF THE DRAWINGS

The present invention will be described in further detail below, with reference to the
25 accompanying drawings, of which

Fig. 1 is a block diagram indicating the steps of a method according to one embodiment of the invention;

Fig. 2 is a schematic illustration of a first embodiment of the system according to the invention;

30 Fig. 3 is a schematic illustration of veins and arteries forming a part of the vascular system of a human being; and

Fig. 4 illustrates schematically how the catheter is arranged in the arteria subclavia dexter, in a second embodiment of the system according to the invention.

35 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method, a system and a set of disposable equipment components for controlling the temperature of a selected brain hemisphere. The method according to the invention in its most general form comprises the steps of using a perfusion pump to

- circulate, extra-corporeally, venous blood from a patient through a heat exchanger to regulate the temperature of the blood by cooling or heating it;
- reintroduce cooled or heated blood into the patient through an artery leading blood to a selected brain hemisphere, the blood in turn modifying the temperature of the selected brain hemisphere;
- maintain circulation and temperature control of the blood until the desired temperature control of the brain hemisphere has been accomplished, and for a desired period of time thereafter.

The venous blood is extracted from a suitable vein, preferably the vena femoralis, by means of a blood extraction device. A device for the reintroduction of blood into the body is inserted, preferably into an artery supplying blood to the selected brain hemisphere, to regulate the temperature of that brain hemisphere.

The blood preferably also passes through an oxygenator to oxygenate the blood. In different embodiments, this oxygenation is carried out before or after temperature regulation.

Below, the invention will be explained by reference to examples of embodiments thereof, primarily relating to cooling a selected brain hemisphere in conjunction with treatment of a case of stroke in a human patient, and it is obvious to a person skilled in the art that the invention can be adapted to different uses within the scope of the independent claims.

It may be noted that a selected brain hemisphere is cooled primarily in relation to the choice of artery into which the cooled blood is introduced, but a secondary cooling of the entire brain also takes place, as a result of the blood flow between the hemispheres.

25 System and method for the treatment of stroke

Figs. 1, 2 and 3 illustrate an embodiment of the system and the method according to the invention. The system according to the invention also comprises a set of disposable components, packaged in a kit. The system according to the invention is explained by reference to the general steps of the method; in different embodiments these steps can be executed in different order. A first embodiment comprises the steps of:

1. Percutaneous insertion of a first catheter into the vena femoralis

A device for the extraction of venous blood, preferably in the form of an introducer or a first catheter, is inserted percutaneously into for example the patient's vena femoralis, to extract venous blood from the patient. Some other vein may be used to extract venous blood, but the vena femoralis is suitable because it is fairly large and is easily reached for percutaneous attachment of a blood extraction conduit. This first catheter preferably has an outer diameter smaller than the normal inner diameter of the vena femoralis, so as not to stop entirely the flow of venous blood around the introducer, but large enough to give a sufficient flow of extracted blood. For an adult patient an outer diameter of approximately

8 - 14 French (F) and an inner diameter as large as possible in relation to the outer diameter would be suitable. For children or grown-ups with other vein dimensions, the dimensions of the catheter will obviously have to be modified accordingly. The catheter has a conical extra-corporeal coupling for low flow resistance during perfusion. This coupling is provided with a seal that can be perforated, for example by a guide wire and/or a dilator, to prevent unnecessary bleeding. The seal can also be removed for attachment to an extra-corporeal circuit. Preferably, the catheter is heparinized internally and externally, to counteract coagulation of the blood that comes into contact with the catheter.

2. Percutaneous entry of a catheter into the arteria carotis communis

10 A device for the reintroduction of blood, preferably in the form of a second catheter, is entered percutaneously into the arteria femoralis, to return cooled blood to the patient. This second catheter, like the first one, has a conical extra-corporeal coupling for low flow resistance during perfusion. This coupling is provided with a seal that can be perforated, for example by a guide wire and/or a dilator, to prevent unnecessary bleeding.

15 The seal can also be removed for attachment to an extra-corporeal circuit. Using a guide-wire, the second catheter is guided according to prior art, from the arteria femoralis via the aorta and the aortic arch to the arteria carotis communis, sinister or dexter, which supplies the selected brain hemisphere with blood. The second catheter is preferably placed caudally of the branching of the arteria carotis interna and the arteria carotis externa. In an

20 alternative embodiment, to be used if for some reason it is impossible or undesirable to enter via the arteria femoralis, the second catheter is inserted in the arteria carotis communis via an artery in the axilla.

The placement of the second catheter in the arteria carotis communis is preferably carried out manually, using angiography to indicate the position of the catheter, but

25 obviously any other suitable method of fluoroscopy can be applied. When the distal open end of the second catheter has reached the correct position in the arteria carotis communis, the guide wire is retracted, which leaves the second catheter ready for attachment to the extra-corporeal blood conduit.

The second catheter is preferably heparinized internally and externally, to

30 counteract coagulation of the blood that comes into contact with the catheter. The arterial catheter further has an outer diameter which is less than the inner diameter of the artery, so as not to block the normal arterial blood flow completely, but large enough to secure a satisfactory supply of temperature-regulated blood to the brain hemisphere. For an adult patient an outer diameter of approximately 8 - 14 French (F) and an inner diameter as large

35 as possible in relation to the outer diameter would be suitable. The length of the second catheter should be sufficient to reach the carotis communis from the arteria femoralis, which for an adult patient corresponds to about 60 to 100 cm. Just as for the first catheter, the dimensions of the second catheter should be adapted when applying the invention to patients of other body sizes.

In addition to the supply of blood of lowered temperature to the patient, other substances may be injected into the brain hemisphere, through a lateral opening provided for this purpose in the extra-corporeal part of the arterial catheter. Such substances might for example be contrast medium for the fluoroscopic observation of the flow of the supplied blood, or substances that influence the condition of the intra-cerebral arteries, for example drugs like heparin and fibrinolytic substances.

3. Attachment of the venous catheter and the arterial catheter to an extra-corporeal blood conduit

10 The inlet of a blood conduit such as a blood tube is attached according to prior art to the other opening of the venous catheter, and the tube is passed through a perfusion pump. The blood tube preferably consists of an internally heparinized biocompatible plastic material, and has a diameter suited to its purpose. The blood tube passes through a circulation pump according to prior art, a so called perfusion pump, preferably equipped
15 with rollers exerting a peristaltic effect externally on the tube.

The blood tube extends from the pump to a heat exchanger, which in this particular embodiment is arranged for cooling the blood, but which in another embodiment may be arranged for heating it. In one type of heat exchanger the blood tube passes through a device which supplies or removes heat energy from the blood through the walls of the
20 blood tube. In another type of heat exchanger, the blood tube is attached to a heparinized heat-exchanging bag with blood canals, providing a large surface area for heating/cooling. In the embodiment intended for the treatment of stroke, the heat exchanger should be capable of cooling blood to a temperature between 0 and 37°C. In some cases, a small temperature fall of only a few degrees is desirable, for example a cooling to 34°C, whereas
25 in other cases a larger temperature fall is desirable, such as down to 0–5°C. Within other areas of application, a heating of the blood may be desirable, such as from 37°C to 40–42°C. As the selected brain hemisphere is cooled/heated, the general body temperature also falls/rises, and accordingly the temperature of the venous blood extracted. The heat exchanger therefore must be controlled so as to keep the blood returned to the body after
30 cooling/heating at the desired temperature.

Optionally, the blood conduit may be attached to an oxygenator according to prior art, before or after the heat exchanger, in order to oxygenate the blood, preferably to a level equivalent to that of arterial blood.

One outlet end of the extra-corporeal blood circuit is attached to the proximal end
35 of the arterial catheter reaching into the arteria carotis communis, from the heat exchanger or in relevant cases from the oxygenator, which completes the configuration of the temperature controlling system and makes it ready for use.

In the description above, the circulation pump has been assumed to be placed in the proximity of the place of extraction of venous blood, but it can also be placed elsewhere in

the extra-corporeal blood circuit, for example immediately before the blood return catheter. In such a case, the rest of the blood conduit should be primed before start with isotonic solution.

In one embodiment of the invention, an open reservoir containing, for example, priming solution or blood, is arranged between the venous catheter and the circulation pump, and a shunt, in the form of an internally heparinized blood tube, has been arranged extra-corporeally to create a connection from one section between the venous catheter and the reservoir to another section between the arterial catheter and the heat exchanger/oxygenator. By closing the flow of blood to/from the vein and opening the flow from the artery, blood will flow out of the arterial catheter, and will be pumped by the circulation pump to the reservoir, whereby the system will be purged of any air present. Any air present on the venous side can then be removed similarly by stopping the flow of blood to/from the artery and using the circulation pump to make the venous blood flow to the reservoir. When the system has been purged of air, the blood flow through the shunt is stopped, for example by means of an artery forceps, and the circulation of blood, according to the description below, can be started.

A kit containing disposable articles comprises one or several blood tubes according to the specifications above, configured to be attached to the inlet and the outlet sides, respectively, of the blood extraction/return devices, a circulation pump, a heat exchanger, an oxygenator and blood extraction/return devices.

4. Circulating blood through the extra-corporeal blood circuit while cooling and optionally oxygenating it

When the system for temperature control has been configured, circulation of blood through the extra-corporeal circuit is started, involving the extraction of venous blood from the vena femoralis, cooling it to the desired temperature in the heat exchanger, for example to a temperature between 0 and 37°C, optionally oxygenating it in the oxygenator, and finally reintroducing it into the patient via the arteria carotis communis, sinister or dexter. The cooled blood flows from there into the selected brain hemisphere, which is cooled swiftly and efficiently.

5. Percutaneous arrangement of a thermistor in the vena jugularis interna

To support a good regulation of the temperature, a temperature sensor, a so called thermistor, is placed percutaneously in a vena jugularis interna in the same lateral body half as the selected brain hemisphere. Through the vena jugularis interna, the blood is transported away from the brain, and the thermistor gives off a signal that reflects the temperature of the blood leaving the brain, thus indicating the temperature of the brain hemisphere being thermally regulated. The thermistor preferably consists of some suitable disposable material, which preferably is heparinized. The dimensions of the part inserted

into the vena jugularis interna should be small enough to prevent any significant obstruction of the venous blood flow.

The output of the thermistor may be used in different ways. In one embodiment, the signal is transferred to a regulator, which controls the heat exchanger or the circulation pump or both, in order to achieve a regulated temperature level in the selected brain hemisphere. Alternatively, or in addition, the signal may be transferred to an indicating device, such as a visual display showing the current temperature of the blood in the vena jugularis interna, and hence the approximate temperature of the selected brain hemisphere.

10 In a second embodiment of the invention, the device for returning the blood, preferably consisting of a heparinized and hydrophilic catheter, is inserted percutaneously into the arteria radialis, dexter or sinister, and positioned in the arteria subclavia, dexter or sinister, according to which hemisphere of the brain is chosen for thermal regulation (see Fig. 4). The said device for returning the blood is preferably a catheter with a diameter
15 corresponding to 1- 10 F, preferably 4- 8 F. In addition, the extra-corporeal part of the said device for returning the blood is capable of being attached to the said blood conduit and hence to the said circulation pump. According to the description above, the pump is set up to circulate the blood through the blood conduit, from the blood extraction device to the blood return device via a heat exchanger, resulting in the return of thermally regulated
20 blood to the patient. The blood conduit may also be attachable to an oxygenator, which enables oxygenation of the blood, and to a reservoir, in which the extracted blood may be mixed with some other solution, containing for example Ringer's acetate solution and drugs, before being returned to the patient. To achieve a quick thermal regulation of the selected brain hemisphere, the perfusion may initially consist of some perfusion solution,
25 such as Ringer's acetate, containing an antioxidant or a drug, followed in a second stage by thermally regulated blood which is returned to the patient. According to this second embodiment, a compression cuff, such as a tourniquet or the like, is placed on the arm in question, i.e. the arm into which the device for returning the blood is inserted, in order to suppress peripheral circulation and to increase the pressure in the blood vessel, making the
30 pressure of the returning blood equal to the pressure exerted by the heart on the blood, which in consequence results in a flow velocity of 10- 12 ml/s. The flow velocity may optionally be regulated in such a way as to make the blood in the arteria vertebralis dexter and the arteria carotis dexter perfuse with a spill-over to the arcus aortae, the flow along the aorta curvatura major being laminar. This is desirable in order to allow the maximum share
35 of the spill-over to reach the aorta carotis sinister. The above arrangement will prevent flow backwards toward the valvular section.

As soon as the thermal regulation has started, diagnostic work can be initiated, such as magnetic resonance imaging, or some other form of diagnostic examination, without having to abort the thermal regulation as described above. When the periferal blood has

reached the desired temperature, for example 32°C, the thermal regulation described is aborted, and the temperature reached can be maintained using conventional cooling blankets or the like.

- 5 The present invention has been described above with reference to exemplifying embodiments, and it is obvious to a person skilled in the art that the invention may be modified in other ways within the scope of the appended claims.

CLAIMS:

1. A system for controlling the temperature of a brain hemisphere of a living being, comprising:
 - 5 - a device for extracting blood from a vein;
 - a blood conduit consisting of one or more parts, the first end of which can be attached to the device for extracting blood;
 - a circulation pump, arranged to pump blood through the blood conduit;
 - a heat exchanger, which can be attached to the blood conduit and is arranged to
10 regulate the temperature of blood to a desired temperature; and
 - a device for blood return, which can be attached to the other end of the blood conduit and is arranged to reintroduce blood into the patient through an artery that supplies the selected brain hemisphere with arterial blood.
- 15 2. A system according to claim 1, wherein the blood return device is arranged to reintroduce blood into the patient through the arteria carotis communis, sinister or dexter, which supplies the brain hemisphere with arterial blood.
- 20 3. A system according to claim 1, wherein the blood return device is arranged to reintroduce blood into the patient through the arteria subclava, sinister or dexter, which supplies the brain hemisphere with arterial blood.
- 25 4. A system according to claim 1, further comprising an oxygenator, which can be attached to the blood conduit and is arranged to oxygenate blood to a desired oxygen concentration.
- 30 5. A system according to claim 1, wherein the blood extraction device is a first catheter, preferably arranged to be inserted into the vena femoralis, having an outer diameter of approximately 8 to 14 French.
- 35 6. A system according to claim 1, wherein the blood return device is a second catheter, preferably arranged to be inserted into the arteria femoralis and extending through the aorta and the aortic arch up to the selected arteria carotis communis, having an outer diameter of approximately 8 to 14 French.
7. A system according to claim 1, wherein the blood return device is a catheter, preferably arranged to be inserted through the arteria radialis and extending to the arteria subclavia.

8. A system according to claim 1, wherein the blood return device further comprises a lateral opening, arranged for the injection of liquid into the selected brain hemisphere.
9. A system according to claim 1, wherein the said blood extraction device and the said blood return device further comprise a conical extra-corporeal coupling, providing low flow resistance during perfusion and fitted with a seal.
10. A system according to claim 1, further comprising a temperature sensor, arranged to be entered percutaneously into the vena jugularis interna on the same lateral body half as the selected brain hemisphere.
11. A system according to claim 7, wherein an output signal from the temperature sensor is transferred to a regulator, arranged to regulate the heat exchanger and/or the circulation pump in relation to the temperature of the blood in the vena jugularis interna and a set value.
12. A system according to claim 7, wherein an output signal from the temperature sensor is transferred to an indicating device, arranged to indicate visually the temperature of the blood in the vena jugularis interna.
13. A system according to claim 1, wherein the heat exchanger is arranged to cool the blood to a temperature in the range of 0–37°C.
14. A system according to claim 1, wherein the heat exchanger is arranged to heat the blood to a temperature in the range of 37–42°C.
15. A method for controlling the temperature of a brain hemisphere of a living being, comprising the steps of:
 - extracting venous blood;
 - thermally regulating the blood extra-corporeally; and
 - reintroducing the thermally regulated blood into an artery supplying the brain hemisphere with arterial blood.
16. A method according to claim 15, wherein the thermally regulated blood is reintroduced through the arteria carotis communis, sinister or dexter, which supplies the selected brain hemisphere with arterial blood.
17. A method according to claim 15, wherein the thermally regulated blood is reintroduced through the arteria subclavia, sinister or dexter, which supplies the selected brain

hemisphere with arterial blood.

18. A method according to claim 15, wherein the venous blood is extracted from the vena femoralis.
- 5
19. A method according to claim 15, wherein the blood is returned to the selected arteria carotis communis by means of a second catheter, inserted into the arteria femoralis and extending through the aorta and the aortic arch.
- 10
20. A method according to claim 15, wherein the blood is returned to the selected arteria subclavia by means of a catheter percutaneously inserted into the arteria radialis.
21. A method according to claim 15, wherein the blood is oxygenated preferably to an oxygen concentration corresponding to that of arterial blood.
- 15
22. A method according to claim 15, wherein the blood is cooled to a temperature in the range of 0–37°C.
23. A method according to claim 15, wherein the blood is cooled to a temperature of 32°C.
- 20
24. A method according to claim 15, applied to a brain hemisphere exposed to a stroke, wherein the blood is cooled and circulated until medical measures have been taken and/or until the ischaemic part of the brain has recovered.
- 25
25. A method according to claim 15, wherein the blood is heated to a temperature in the range of 37–42°C.

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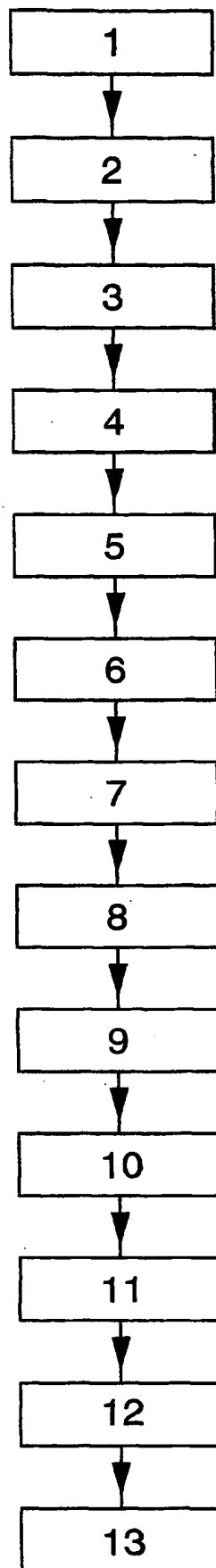


Fig. 1

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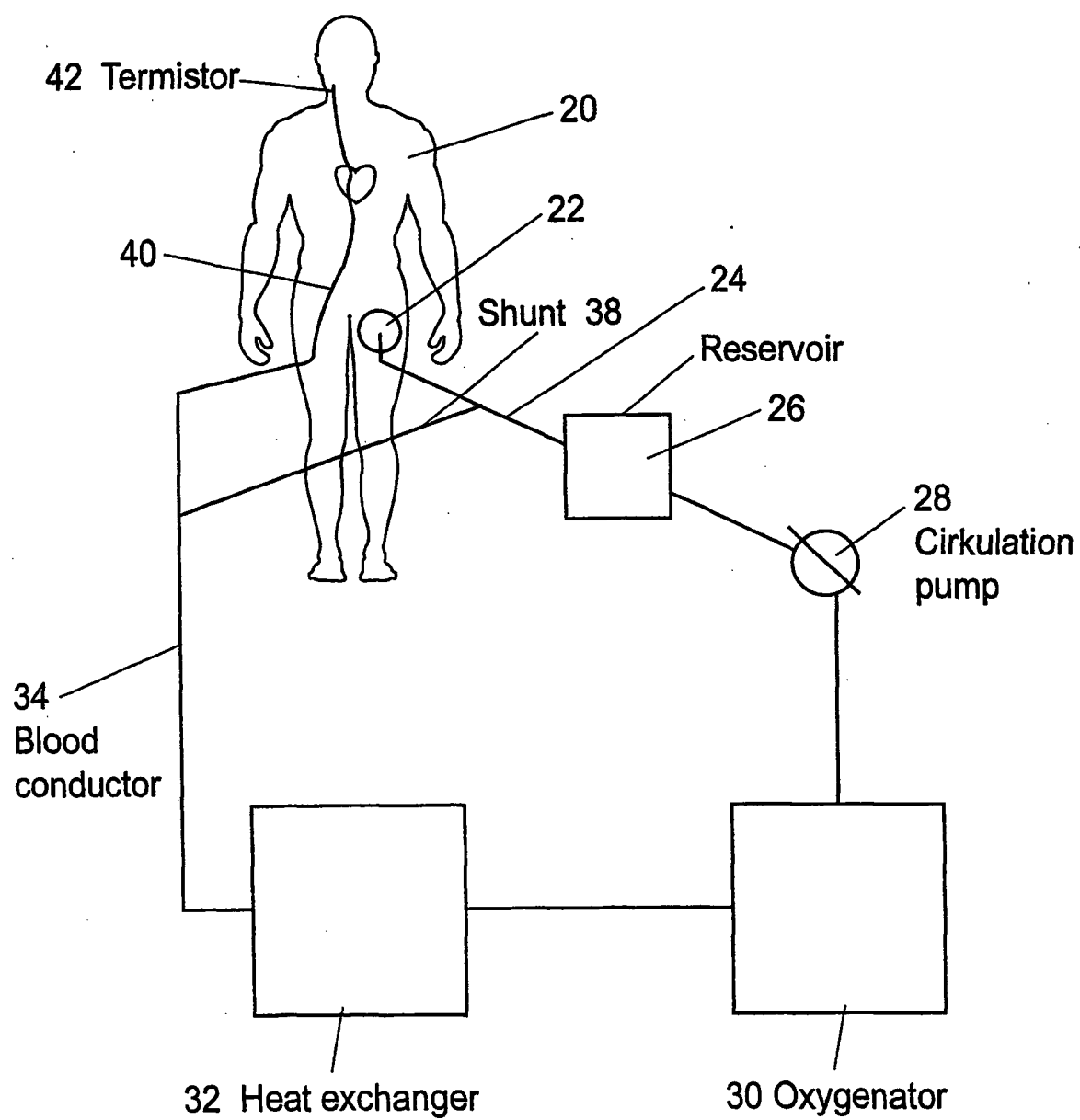


Fig. 2

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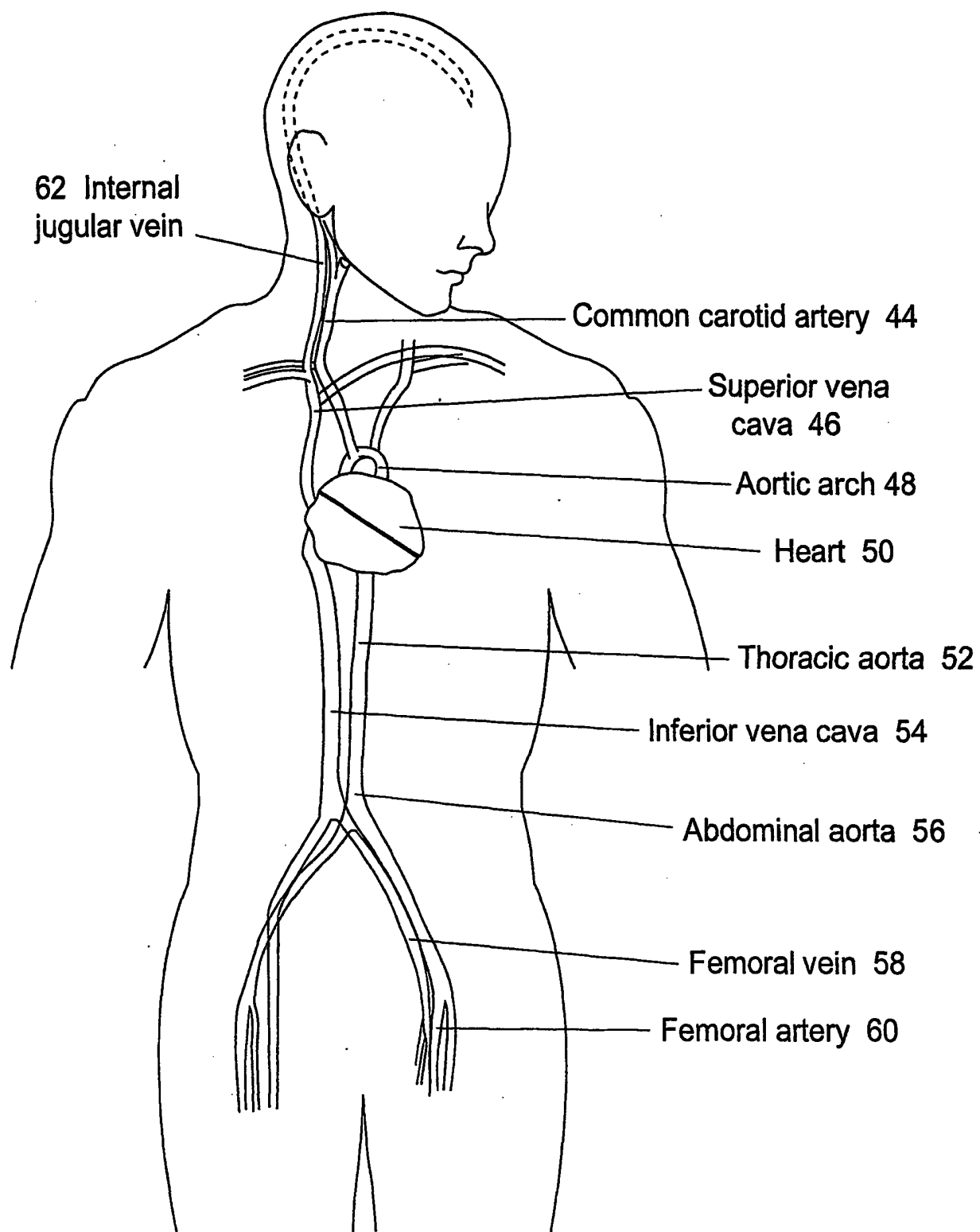


Fig. 3

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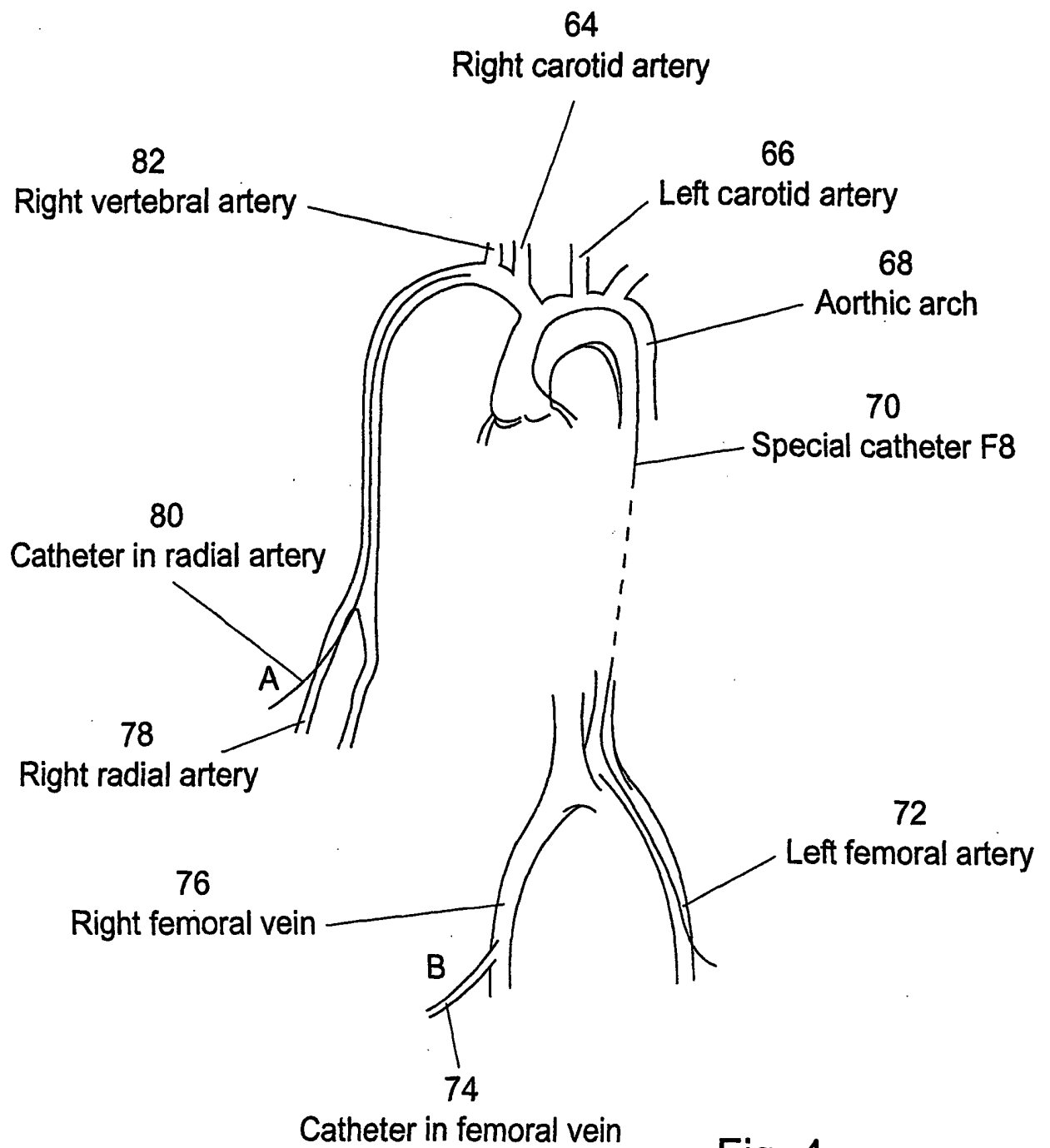


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01259

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61M 1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61M, A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6042559 A (JOHN D. DOBAK, III), 28 March 2000 (28.03.00), column 2, line 35 - column 4, line 3, figure 1, abstract --	1-14
A	US 5391142 A (J.P. SITES ET AL.), 21 February 1995 (21.02.95), column 2, line 35 - column 3, line 34, figures 2,4, abstract -- -----	1-14



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28 Sept 2001

Date of mailing of the international search report

02 -10- 2001

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INTERNATIONAL SEARCH REPORT
Information on patent family members

03/09/01

International application No.

PCT/SE 01/01259

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6042559 A	28/03/00	NONE	
US 5391142 A	21/02/95	AU 4995693 A WO 9403216 A	03/03/94 17/02/94

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01259**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **14-25**
because they relate to subject matter not required to be searched by this Authority, namely:
Method for treatment of the human or animal body by surgery or therapy. See PCT Rule 39.1(iv).
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.